REMARKS/ARGUMENTS

Claims 1-9, 13-32, directed to the following species: 1) BCG and interferon-γ, or LPS, TNF-α as maturing agent, and 2) CD86 or CD80 co-stimulatory molecule have been examined in the instant application. In the present response all remarks are directed to the currently elected species although certain claims have not been amended to cancel the non-elected subject matter. Should the generic claims be found allowable, Applicants again respectfully requests rejoinder of a reasonable number of non-elected species as set forth in M.P.E.P. § 821.04.

Claim 1 has been amended as described in detail below. No new matter has been added by this amendment. The Examiner is respectfully requested to reconsider the pending claims in view of above amendments and the remarks below.

Rejections Under 35 USC § 102:

Claims 1 through 3, and 5 and 13 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Triozzi *et al., Cancer* 89:2646-2654, 2000, and as evidenced by Labeur *et al., J. Immunol.* 162:168-175, 1999. The Examiner has considered Applicants prior response but has not found it persuasive. In particular, the Examiner has alleged that the instant specification discloses as follows "In DCs cultured and partially matured according to the present invention in the presence of a dendritic cell maturation agent, such as GM-CSF and IL-4, the levels of phosphorylated JAK2 (janus activated kinase 2) can be measured to indicate the initiation of maturation by methods well known in the art". The Examiner has also asserted that although Sallust *et al.* name human DCs cultured in GM-CSF and IL-4 differently, for example, as immature DCs, however, when based on the above disclosure in the instant application, it would be reasonable to interpret the human DCs treated with GM-CSF and IL-4 taught by Triozzi *et al.* as partially matured DCs.

Further, the Examiner has alleged that it is reasonable to interpret human DCs treated in GM-CSF and IL-4, taught by Triozzi *et al.*, as partially mature DCs and not mature DCs based on: 1) the teaching of Labeur *et al.* that murine DCs treated in GM-CSF and IL-4 have intermediate degree of maturation, in between the immature murine DCs treated with only GM-CSF and the more mature DCs treated in GM-CSF and IL-4 plus LPS or CD40L, and especially 3) the ability of those murine DCs treated with GM-CSF and IL-4 to take up and process antigen, in addition to antigen presentation, and T cell stimulation, in view of the teachings of Labeur *et al.*

The Examiner also asserts that Applicants' prior response does not have any evidence or recite any reference teaching that the murine DCs treated with GM-CSF and IL-4 taught by Labeur *et al.* are mature DCs and do not represent a model for human DCs treated with GM-CSF and IL-4. In addition, the Examiner alleges that contrary to the response assertion, murine DCs treated with GM-CSF and IL-4 taught by Labeur *et al.* retain the ability to take up and process antigen and show that when incubated with an antigen, the OVA peptide, murine DCs treated with GM-CSF and IL-4 are intermediate between immature murine DCs treated GM-CSF alone and more matured murine DCs treated with GM-CSF and IL-4 plus LPS or DC40L in the ability to present antigen. From these alleged teachings the Examiner concludes that murine DCs treated with GM-CSF and IL-4 must inherently have been able to pick up and process the antigen present in the incubation medium in order to present the antigen. Further, the Examiner alleges that based on Figure 3 and page 171, second column, of Labeur *et al.* and the disclosure in the specification, it is reasonable to interpret that murine DCs treated with GM-CSF and IL-4, and more matured DCs treated with GM-CSF and IL-4 plus LPS or CD-40 taught by Labeur *et al.* are all partially mature, because they still retain the ability to pick up and process antigen. Finally, the Examiner alleges that as DCs treated with GM-CSF and IL4 taught by Triozzi *et al.* and abeur *et al* are the same as the claimed partially mature DCs, the method of treating cancer using DCs treated with GM-CSF and IL-4 prior to their administration into a patient as taught by Triozzi *et al.* is the same as the claimed method.

Applicants must strongly disagree with the rejection of claims 1-3, 5 and 13 under 35 U.S.C. § 102(a) as being anticipated by Triozzi *et al.* and as evidenced by Labeur *et al.* In particular, contrary to the allegation by the Examiner the specification as filed does not teach that GM-CSF and IL-4 are maturation agents. While the Examiner is correct a sentence appears at page 11, second paragraph, listing GM-CSF and IL-4 as maturation agents, the statement is merely a typographical and/or clerical error that would be recognized by the skilled artisan. The combination of GM-CSF and IL-4 is clearly defined as one of several differentiation agents for certain dendritic precursor cells. See for example, page 2, lines 28-30 ("DCs exist in peripheral tissues in an immature form, ready to take up and process antigen. It is this immature cell that is most closely mimicked by the DCs generated from monocytes in the presence of GM-CSF and IL-4."), page 6, line 19 through page 10, line 7 (In particular page 9, lines 16-27, wherein GM-CSF and IL-4 are described as dendritic cell differentiation agents.), page 11, lines 1-4, and the examples. Dendritic cell maturation agents are defined in the specification as filed at, for example, page 10, lines 8-27. Still further, the characteristics of, and differences between, immature and mature DCs can be found in the specification at page 11, lines 16-30. The Examples in the specification show that murine bone marrow dendritic cell precursors are clearly different than the dendritic cells treated with a dendritic cell maturation agent. In particular, example 1 shows that monocytic dendritic dell precursors isolated by tangential flow filtration and differentiated in GM-CSF alone and subsequently contacted with the dendritic cell maturation agents BCG and IFNγ differ in their ability to uptake and process tumor cell antigen. See page 15, Table 1. Further, Examples 2 and 3 show that murine bone marrow cells, subsequent to red cell lysis, and incubated with murine GM-CSF and IL-4 did not resolve xenogenic tumor as well as similar differentiated bone marrow cells subsequently partially matured with BCG and IFNγ. Applicants clearly did not intend the combination of GM-CSF and IL-4 to be considered dendritic cell maturation agents as alleged by the Examiner.

As such, Applicants prior argument regarding Triozzi *et al.* and Labeur *et al.* are relevant to the present rejection. In particular, Triozzi *et al.* do not use partially mature dendritic cells in the methods disclosed, but instead use immature dendritic cells differentiated from

monocytes by culture in GM-CSF and IL-4. This method of generating immature dendritic cells from monocytes is well known to the skilled artisan. For example, Sallusto and Lanzavecchia, *J. Exp. Med.* 179:1109-1118, 1994, clearly demonstrated that monocytes when cultured in the presence of GM-CSF and IL-4 differentiate into immature dendritic cells. In addition, as above, the present specification demonstrates that murine bone marrow cells, cultured in the presence of GM-CSF and IL-4 are not the same as those same cells contacted with a dendritic cell maturation agent in regard to ability to uptake tumor antigen or ability to reduce the growth of xenogenic tumor when administered to a mouse.

Labeur *et al.* cited by the Examiner does not conflict with the teaching of Sallusto and Lanzavecchia. In particular, Labeur *et al.* induce the differentiation of dendritic cells from murine bone marrow dendritic cell precursors. It is well known in the art that the cytokines necessary to induce the differentiation of human immature dendritic cells and/or human mature dendritic cells from human monocytic dendritic cell precursors are different from those necessary to induce differentiation of murine immature dendritic cells and/or murine mature dendritic cells from murine bone marrow dendritic cell precursors. Labeur *et al.* demonstrate that bone marrow dendritic cell precursors from mice are induced to differentiate into immature dendritic cells by culture in GM-CSF alone. Culture of the bone marrow dendritic cell precursors in GM-CSF and IL-4 induced the cells to differentiate and mature as measured by cell surface phenotype and the substantial reduction in phagocytosis and endocytosis. The phenotype of dendritic cells produced by Labeur *et al.* by culture in GM-CSF and IL-4 differ only in the stimulus of mixed lymphocyte reactions and efficiency of *in vitro* peptide presentation when compared with bone marrow dendritic cell precursors cultured in the presence of GM-CSF and IL-4 with TNF-α, LPS or CD40L. Labeur *et al.* specifically state that IL-4 "is a potent enhancer of mouse DC maturation". See page 173, right column, last paragraph, lines 6-7. As such, Labeur *et al.* does nothing to support the characterization by the Examiner of the dendritic cells used by Triozzi *et al.* being partially mature dendritic cells.

In addition, the Examiner has noted that "fully mature DCs exposed to GM-CSF plus IL-4 and CD40L, taught by Labeur et al(Labeur *et al.*, abstract), that have the ability to pick up and process antigen, are interpreted as partially matured DCs. Applicant has reviewed the abstract of Labeur *et al.* and only find the following statements regarding intermediate dendritic cell maturation: "Whereas cells cultured in GM-CSF alone were functionally immature, cells incubated in CD40L or LPS were mature BmDC, as evident by morphology, capacity to internalize Ag, migration into regional lymph nodes, IL-12 secretion, and alloantigen or peptide Ag presentation in vitro. The remaining cultures exhibited intermediate dendritic cell maturation." See Labeur *et al.* abstract, lines 6-9. Applicant strongly disagrees that this statement supports the Examiner's conclusion that the DCs produced by Labeur *et al.* have the ability to pick up and process antigen and therefore should be interpreted to be partially mature DCs. In fact, Labeur *et al.* teach that bone marrow DCs induced by culture in GM-CSF and IL-4 do not retain the ability to take up and process antigen. Table II, at page 171, clearly shows that BmDCs cultured in GM-CSF and IL-4 have a substantially reduced ability to uptake antigen and have essentially the same capacity for phagocytosis as those BmDCs cultured in the presence of GM-CSF and IL-4 plus LPS or CD40L. At page 171, right had paragraph beginning at line 1 of the text, the authors explain the data as follows: "Incubation of cells with IL-4 resulted in a marked down regulation of FITC-*E. coli* uptake. Further addition of Flt3L, TNF-α, CD40L, or LPS did not have additional effects on phagocytosis". As such, even if the culture of monocytic dendritic cell precursor cells in GM-CSF and IL-4 could be directly compared with the culture of murine bone marrow dendritic cell precursor cells in GM-CSF and IL-4, the teachings of Labeur *et al.* are not supportive of the conclusion of the Examiner that the dendritic cells of Labeur *et al.* or Torizzi *et al.* are partially mature dendritic cells as defined and used in the present application and claims. Finally, Applicant shows in the Examples presented in the specification as filed that murine bone marrow cells cultured in the presence of GM-CSF and IL-4 differ in their ability to uptake and process tumor antigen when compared with murine bone marrow cells partially matured by contact with BCG and IFNγ.

Applicant believes that the claims 1-3, 5 and 13 are not anticipated by Torizzi *et al.* in view of Labeur *et al.* As such, Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claims 1-3, 5 and 13 as being anticipated by Torizzi *et a.* in view of Labeur *et al.*

Rejections Under 35 USC § 103:

Claims 2 and 4 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.* (above) in view of Labeur *et al., J. Immunol.* 162:168-175, 1999, *supra*, and further in view of Murphy *et al.* (US 5,788,963). The prior response of Applicant has been considered by the Examiner, but has been deemed unpersuasive. In particular, as above, the Examiner believes that DCs treated with GM-CSF and IL-4 taught by Triozzi *et al.* and Labeur *et al.* are the same as the claimed partially mature DCs. As such, the Examiner alleges that that method of treating cancer using DCs treated with GM-CSF and IL-4 prior to their administration into a patient as taught by Triozzi *et al.* is the same as the claimed method. Further, the Examiner alleges that it would be *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to obtain DCs taught by Triozzi *et al.* and Labeur *et al.* from skin, spleen, bone marrow, thymus, lymph nodes, umbilical cord blood, as taught by Murphy *et al.* to increase the number of available sources for making DCS. Further, the Examiner alleges that to replace the DCs obtained from the individual to be treated, taught by Triozzi *et al.* and Labeur *et al.* with DCs isolated from a healthy HLA matched individual as taught by Murphy *et al.* to increase the number of available DCs and that it HLA-matched DCs would be necessary, because antigen presentation of DCs is restricted to the complementing HLA molecule in view of the teachings of Murphy *et al.*.

Applicant strongly disagrees with the allegations and assertions of the Examiner. As above, Triozzi *et al.* do not teach the administration of partially mature DCs, but instead teach the administration of immature DCs differentiated from monocytic dendritic cell precursors by

the standard method of culturing the monocytic dendritic cell precursors in the presence of GM-CSF and IL-4. Labeur *et al.* do not add anything to the disclose of Triozzi *et al.* that discloses or suggests either the administration of partially mature dendritic cells to a patient or the use of partially mature DCs isolated or differentiated from precursor cells isolated from any source. As above, Labeur *et al.* teach that murine bone marrow dendritic cell precursors cultured in the presence of GM-CSF and IL-4 differentiate into dendritic cells that have a significantly reduced ability to up take and process soluble antigen. The dendritic cells produced by the method of Labeur *et al.* also differ in their ability to induce an anti-tumor response when compared with bone marrow dendritic cell precursor maturation agents, such as LPS or CD40L, but not in the ability to up take and process antigen. The specification also shows in the Examples that murine bone marrow dendritic precursor cells cultured in the presence of GM-CSF and IL-4 are different from those subsequently cultured in the presence of a dendritic cell maturation agent as defined in the present specification. Table 1 of the specification shows that bone marrow dendritic precursors cells cultured in the presence of a dendritic cell maturation agent subsequent to culture in GM-CSF and IL-4 were better at antigen uptake as measured by either the percentage of cells that take up antigen or by the amount of material picked up.

The addition of Murphy *et al.* adds nothing to provide the missing elements from Triozzi *et al.* and/or Labeur *et al.* when consider either alone or in any combination. Therefore, as the Examiner has failed to establish a *prima facie* case for obviousness Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 2 and 4 as being unpatentable over Triozzi *et al.* in view of Labeur *et al.*, and further in view of Murphy *et al.*

Claims 6 through 9 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.* (above) in view of Labeur *et al. J. Immunol.* 162:168-175, 1999 (*supra*) and further in view of US 20050059151 (Bosch *et al.*), and Chakraborty *et al., Clin. Immunol.* 94:88-98, 2000). The Examiner has considered Applicant's prior response but considers it unpersuasive. In particular, the Examiner alleges that the DCs treated with GM-CSF and IL-4 taught by Triozzi *et al.* and Labeur *et al.* are the same as the claimed partially mature

DCs, as set forth above. As such, the method of treating cancer taught by Triozzi *et al.* is the same as the claimed method, wherein the DCs treated with GM-CSF and IL-4 are administered into a patient, without prior exposure of the DCs to a tumor antigen. Further, the Examiner alleges that although Bosch *et al.* use treated DCx that have been exposed to antigen prior to their administration to a subject, the primary reference, Triozzi *et al.* teach the use of treated DCs for administration into a cancer patient, without the need of their exposure to a cancer antigen.

Therefore, the Examiner alleges that it would have been *prima facie* obvious for one of ordinary skill in the art at the time the present invention was made to add to GM-CSF plus IL-4 maturing agent as taught by Triozzi *et al.* and Labeur *et al.* BCG and interferon γ as taught by Bosch *et al.* in the method taught by Triozzi *et al.* and Labeur *et al.* for maturing DCs *in vitro* for use in producing an anti-cancer response because 1) a combination of BCG and interferon γ selectively produces more maturing DCs that secrete IL-12 than those inhibiting DCs secreting IL-10, as taught by Bosch *et al.*, 2) DCs that secrete IL-12 efficiently stimulate T cells, whereas DCs that produce IL-10 are inhibitory, as taught by Chakraborty *et al.*, 3) the ability of DCs to promote antitumor immunity correlates with their high efficiency of stimulating resting T cells and high production of IL-12, as taught by Labeur *et al.* The Examiner also alleges, that in other words, BCG and interferon gamma as maturation agent as taught by Bosch *et al.* would be advantageous, because they selectively enhance the production of stimulating DCs that secrete IL-12, and therefore efficiently stimulate T cells, in view of the teaching of Chakraborty *et al.*, and promoting anti-tumor immunity, in view of the teachings of Labeur *et al.*

Applicant again must strongly disagree with the allegations and assertions of the Examiner. In particular, as above, Triozzi *et al.* does not disclose or suggest a method of administering partially mature DCs that have not been contacted with antigen *in vitro*. In addition, Labeur *et al.* also do not disclose or suggest such a method. Further, Bosch *et al.* and/or Chakraborty *et al.* do not disclose or suggest any element missing from the teachings of Labeur *et al.* to render obvious any of claims 1 and 6-9. Even if either Bosch *et al.* and/or Chakraborty *et al.* were to teach or suggest those elements alleged by the Examiner above, any

combination of those references with Triozzi *et al.* and/or Labeur *et al.* either alone or in any combination would not result in the present invention. If the references were combined as suggested by the Examiner, at most, the skilled artisan might use a maturation agent suggested by Bosch *et al.* to mature DCs that had been exposed to antigen prior to administration to a subject. That is not the invention as recited in any of claims 6 through 9. The addition of Chakraborty *et al.*, which is alleged by the Examiner to teach the secretion of IL-12 by certain dendritic cells, provides nothing that would disclose or suggest the present invention. In particular, Chakraborty *et al.* provides no information about how dendritic cells that have not been allowed to complete maturation would respond when administered to a patient. As such, neither Triozzi *et al.* and/or Labeur *et al.* when considered alone or in any combination with Bosch *et al.* and/or Chakraborty *et al.* do not disclose or suggest the invention as recited in claims 6 through 9.

Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claims 6 through 9 as being unpatentable over Triozzi *et al.* in view of Labeur *et al.* and further in view of Bosch *et al.* and/or Chakrabory *et al.* in light of the amendments and remarks above.

Claims 14 through 18 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.* (above) in view of Labeur *et al.*, *J. Immunol.* 162:168-175, 1999 for the reasons of record. Applicant's response has been considered and not found persuasive by the Examiner. In particular, as above, the Examiner believes that the DCs treated with GM-CSF and IL-4 taught by Triozzi *et al.* and Labeur *et al.* are the same as the claimed partially mature DCs. Further, the Examiner believes that the method of treating cancer using DCs treated with GM-CSF and IL-4 prior to their administration into a patient as taught by Triozzi *et al.* is the same as the claimed method. As such, the Examiner has alleged that it would have been *prima facia* obvious for one of ordinary skill in the art at the time the invention was made to ad,omoster DCs taught by Triozzi *et al.* and Labeur *et al.* to a tissue area surrounding the tumor, into a lymph node directly draining a tumor area, directly to a circulatory vessel duct that delivers

blood or lymph to the tumor or a tumor afflicted organ, or into the circulatory system such that the cells are delivered to the tumor or tumor afflicted organ, to increase the number of available sites for DC injection from which DCs could be readily delivered to the tumor in view of the allegation that DCs migrate inefficiently into the regional lymph nodes after subcutaneous injection, as taught by Labeur *et al.*

Applicant again must disagree with the allegations and assertions of the Examiner. The partially mature DCs of the present claims are not the same as those taught by Triozzi *et al.* GM-CSF and IL-4 are not considered dendritic cell maturation agents by Applicant as set forth above. Further, as above, Example 1 clearly shows that murine bone marrow dendritic precursor cells contact with GM-CSF and IL-4 are not the same as those additionally matured in the presence of a dendritic cell maturation agent, such as a combination of BCG and IFNγ. In addition, Triozzi *et al.* and/or Labeur *et al.* when considered alone or in any combination do not disclose or suggest a method wherein partially matured dendritic cells are administered by any method. Further, contrary to the Examiners allegations, it would not have been obvious to one of ordinary skill to choose direct administration of the presently claimed partially matured DCs over subcutaneous injection. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) of claims 14 through 18 as being unpatentable over Triozzi *et al.* in view of Labeur *et al.* be withdrawn.

Claims 19 and 20 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.* (above) in view of Labeur *et al.*, (*supra*), and further in view of Nikitina *et al.*, *Int. J. Cancer* 94:825-833, 2001. The Examiner has consider the prior response of Applicant but does not find it persuasive. In particular, as above, the Examiner alleges that the DCs treated with GM-CSF and IL-4 taught by Triozzi *et al.* and Labeur *et al.* are the same as the claimed partially mature DCs, as set forth above. As such, the method of treating cancer taught by Triozzi *et al.* is the same as the claimed method. As such, the Examiner has alleged that it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to combine DC administration taught by Triozzi *et al.* and Labeur *et al.* with radiation

therapy, because gamma irradiation induces the dramatic ability of DCs injected i.v. or s.c. to migrate and penetrate cancer tissue, and to take up apoptotic bodies resulting in enhanced potent antitumor responses.

Applicant must again respectfully disagree with the allegations and assertions of the Examiner. As set forth above, the partially mature DCs of the present claims are not the same as those taught by Triozzi *et al.* GM-CSF and IL-4 are not considered dendritic cell maturation agents by Applicant as set forth above. Further, as above, Example 1 clearly shows that murine bone marrow dendritic precursor cells contact with GM-CSF and IL-4 are not the same as those additionally matured in the presence of a dendritic cell maturation agent, such as a combination of BCG and IFNγ. In addition, Triozzi *et al.* and/or Labeur *et al.* when considered either alone or in any combination do not teach the methods or compositions of the present claims. In particular, Triozzi *et al.* does not teach the administration of partially matured DCs, but only teaches the administration of immature DCs that lose their ability to induce an immune response when administered. In addition, the DCs taught in Labeur *et al.* are exposed to antigen *in vitro* prior to administration to an individual and are not the same as the DCs used in the presently claimed methods. Thus, Applicant submits that Triozzi *et al.* and/or Labeur *et al.* even if combined with Nikitina *et al.* fail to teach or suggest each and every element of claims 19 and 20. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) of claims 19 and 20 as being unpatentable over Triozzi *et al.* in view of Labeur *et al.* in further view of Nikitina *et al.* be withdrawn.

Claims 21 through 23, 25 and 27 through 32 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.*, (above) in view of Labeur *et al.* (above) and Sukhatme *et al.* (US 6,797,488). The Examiner has considered the prior response of Applicant, but does not consider it persuasive. In particular, alleges that contrary to the response Triozzi *et al.* do not teach that human DCs treated with GM-CSF and IL-4 are immature DCs and that the DCs treated with GM-CSF and IL-4 taught by Triozzi *et al.* and Labeur *et al.* are the same as the claimed partially mature DCs as set forth above. In addition, the Examiner has alleged that

Triozzi *et al.* teach that DCs generated *in vitro* by GM-CSF and IL-4 express the co-stimulatory molecules CD80 and CD86, and a low number of CD83. Further, the Examiner has alleged that as the non-elected cell surface molecules are not recited as limitations in the claims, and therefore the argument is moot. As above, the Examiner has also raised the issue of passage in the specification as filed that recites GM-CSF and IL-4 as dendritic cell maturation agents as providing support that it would be reasonable to interpret the human DCs treated with GM-CSF and IL-4 taught by Triozzi *et al.* as partially mature DCs.

Applicant must again respectfully disagree with the rejection of the Examiner. The dendritic cells of the present invention are not the same as those of the cited prior art in spite of the passage in the instant specification cited by the Examiner. As above, the passage in the instant specification is clearly an obvious typographical and/or clerical error. The remainder of the specification fully distinguishes the prior art from the partially mature DCs of the present application. In particular, the dendritic cells of Triozzi *et al.* are immature dendritic cells and are not partially matured dendritic cells as set forth in claims 21-23, 25 and 27-32. As set forth in the specification at page 9, line 28 through page 10, line 7 and page 11, lines 5 through 30, immature dendritic cells and partially mature dendritic cells differ in a number of ways including the levels of expression of a number of cell surface antigens CD80 and CD86 recited in the claims. As well as the cell surface molecules CD14, CD11c not recited in the claims. In addition, mature and immature DCs differ in the phosphorylation level of a number of intracellular proteins including for example, jak2. Applicant respectfully directs the Examiner to additional differences in the cell surface phenotype and the levels of IL-10 and/or IL-12 produce by monocytic dendritic cell precursors cultured in the present of GM-CSF and IL-4 and those cultured in the presence of GM-CSF, IL-4 and a dendritic cell maturation agent. Immature dendritic cells induced to mature by the addition of, in this example, IFNγ and SAC are clearly different in the amounts of IL-10 and/or IL-12 produced and in cell surface phenotype. As such, it is clear that the "partially mature" dendritic cells, immature dendritic cells contacted with a dendritic cell maturation agent, as recited in the present claims reciting the cell surface markers CD80 and CD86 do not have the same properties as the dendritic cells of either Labeur *et al.* or

Triozzi *et al.* Applicant also again respectfully directs the Examiner to page 2652, right column, lines 2 through 11 of Triozzi *et al.* where the authors conclude that the immature dendritic cells administered *in vivo* lost the co-stimulatory molecule B7-2 (CD86A) and showed a decrease in the intensity of CD11c suggesting the possibility that immunostimulatory activity typical of dendritic cells was down regulated. Applicant discloses in the specification as filed that the "partially matured" dendritic cells, as claimed, down regulate cytokine receptors on the surface as compared with "immature" dendritic cells making them less sensitive or responsive to any immunosuppressive effects of cytokines in the intratumoral space. Immature dendritic cells as defined in the specification include monocytic dendritic cells cultured in the presence of GM-CSF and IL-4. As such, the "partially matured" dendritic cells of claims 21 through 23 and 27 through 32 are not the same as those taught by Triozzi *et al.* Sukhatme *et al.* is cited by the Examiner as disclosing a pharmaceutical carrier. As Triozzi *et al.* and/or Labeur *et al.* do not teach the "partially mature" dendritic cells of the present invention or methods for their administration, the addition of the teachings of Sukhatme *et al.* does not disclose or suggest the present invention.

Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claims21 through 23, 25 and 27 through 32 under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.*, (above) in view of Labeur *et al.* (above) and Sukhatme *et al.* (US 6,797,488) in view of the remarks above.

Claim 26 remains rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.*, (above) in view of Labeur *et al.*, (above) and Murphy *et al.* (US 5,788,963, *supra*) for the reasons of record. The Examiner has reviewed the prior arguments of Applicant, but does not find them persuasive. In particular, the Examiner believes that the DCs treated with GM-CSF and IL-4 taught by Triozzi *et al.* and Labeur *et al.* are the same as the claimed partially matured DCs as above. As such, the Examiner has opined that it would have been obvious to replace DCs obtained from the individual to be treated, taught by Triozzi *et al.* and Labeur *et al.* with DCs that have been isolated from a healthy individual HLA-matched to the individual to be

treated, as taught by Murphy *et al.*, to increase the number of available DCs, for example, in situations where the patient to be treated cannot provide sufficient DCs, as taught by Murphy *et al.* Further, the Examiner has alleged that an HLA –matched DC would be necessary because antigen presentation of DCs in restricted to the complementing HLA molecule, also in view of the teachings of Murphy *et al.*

Applicant must again disagree with the Examiner. As above, the cited primary references Triozzi *et al.* as demonstrated in Labeur *et al.* are not the same as the claimed partially mature DCs. The partially mature DCs as set forth in the present specification and claims have been induced *in vitro* to begin maturation with a DC maturation agent, not GM-CSF and IL-4. In Triozzi *et al.* immature monocytic derived dendritic cells are administered to a patient, or Labeur *et al.* where DCs contacted with antigen and that have been induced to full maturation as indicated by their substantial loss of the ability to uptake antigen *in vitro* are administered to patients. As such, Triozzi *et al.* and/or Labeur *et al.* when either considered alone or in combination teach neither the administration of partially mature DCs or compositions that comprise partially mature DCs combined with a pharmaceutically carrier, much less the administration of partially mature DCs or compositions comprising partially mature DCs that have been HLA-matched to a patient to be treated as taught by Murphy *et al.* Therefore, any combination of Triozzi *et al.*, and/or Labeur *et al.* with Murphy *et al.*, do not teach or suggest each and every element of dependent claim 26.

In view of the above remarks Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claim 26 under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.*, (above) in view of Labeur *et al.*, (above) and Murphy *et al.* (US 5,788,963, *supra*).

Rejections under 35 USC § 112:

Claims 1-9, 13-32 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. In particular, the Examiner believes that Claims 1-9, 13-32 are indefinite, because claim 1 is confusing. The Examiner has alleged that Claim 1 can be interpreted either as: 1) the partially matured dendritic cells have been induced to mature in vitro, and have become matured dendritic cells in vitro, or 2) the dendritic cells have been induced by a maturation process and have become partially matured *in vitro* before being administered to an individual, wherein said partially matured dendritic cells are capable of taking up and processing antigen *in vivo*, *i.e.*, after being administered to an individual. The Examiner has, for the purpose of compact prosecution, interpreted claim 1 as:

A method for producing an anti-tumor immune response comprising administration to an individual with a cancerous tumor a cell population comprising partially matured dendritic cells that have been induced to partially mature *in vitro*, wherein the partially matured dendritic cells take up and process antigen in vivo and are enabled to induce an anti-tumor immune response subsequent to administration to the individual.

Applicant thanks the Examiner for proceed with prosecution in spite of her belief that claim 1 is indefinite. Although Applicant does not believe claim 1 to be indefinite, but in order to further expedite prosecution, claim 1 has been amended to recite ". . . administration to an individual with a cancerous tumor a cell population comprising partially matured dendritic cells that have been induced to ~~mature~~ initiate maturation *in vitro*, wherein the partially matured dendritic cells take up and process antigen *in vivo* and are enabled to induce an anti-tumor immune response subsequent to administration to the individual." Applicant believes that the amendment merely clarifies that the partially mature dendritic cells have not completed maturation prior to administration.

The Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1-9, 13-32 stand rejected under 35 U.S.C. § 112, second paragraph, in view of the above amendments and remarks.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 22 April 2010

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